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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,737	06/29/2001	Paolo Renzi	701826051150	4150

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EXAMINER	
LACOURCIERE, KAREN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/07/2003 14

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/719,737	Applicant(s) RENZI, PAOLO	
	Examiner Karen A. Lacourciere	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-76* is/are pending in the application.

4a) Of the above claim(s) *41, 42, 46-49, 56-67 and 73-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-45, 50-55 and 68-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5, 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

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DETAILED ACTION

Election/Restrictions

Applicant's election of Group IV and SEQ ID NO:9 and 18 in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 41, 42, 46-49, 56-67 and 73-76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

SEQ ID NO: 1-7, 10-16, 20, 22 and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Claim Objections

Claims 53-55 and 70-72 are objected to because the claims recite non-elected sequences, which are non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43-45, 50, 51 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43-45, 50, 51 and 68 are indefinite because they depend from a non-elected claim.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 52-55 and 69-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 52-55 and 69-72 are drawn broadly to methods of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer using a nucleic acid directed to a common subunit of IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against CCR3 receptor. The range of treatments encompassed in the claims are very broad and would encompass treatments for generally any type of cancer, any disease involving inflammation in generally any tissue type, generally any allergy, treatments involving nucleic acids delivered by any means, including systemic delivery, as well as aerosol delivery to the lung. The claims are further drawn to pharmaceutical compositions comprising a nucleic acid directed to a common subunit of IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against CCR3 receptor. Claims to compositions have been included in this rejection because as pharmaceutical compositions they are required to have a pharmaceutical effect.

The specification provides examples wherein mice are treated with antisense targeted to a common subunit of IL-3, IL-5 and GM-CSF receptors by aerosol delivery to the lung and the antisense is taken up in the cell. The specification provides a separate example wherein antisense targeted to CCR3 receptor was used to inhibit the expression of the receptor in cell in vitro.

The specification does not present any guidance on what specific types of cancer and inflammatory diseases can be treated or prevented using a nucleic acid directed to a common subunit of IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against CCR3 receptor, and what cells to target for a particular disease or

condition. The specification does not provide specific guidance on how to delivery an effective concentration of antisense to specific cell types for a particular condition systemically. The specification discusses aerosol delivery, however, this type of delivery would only be applicable to a small subset of conditions encompassed by the claims and would not provide guidance for systemic delivery of antisense, as would be required for the majority of cancers, inflammatory conditions and allergies encompassed in the claims, for example. The specification does not demonstrate that two separate oligonucleotides, one targeted to a common subunit of IL-3, IL-5 and GM-CSF receptors and one directed against CCR3 receptor, can be delivered at a high enough concentration to produce any pharmaceutical or treatment effect. The specification does not provide any examples wherein asthma, allergy, hypereosinophilia, general inflammation or cancer are treated or prevented using a nucleic acid directed to a common subunit of IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against CCR3 receptor

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column,

second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed, or to make a pharmaceutical composition with pharmaceutical properties, as claimed. The examples provided by the specification would not provide guidance for the broad methods claimed, as the examples are performed using aerosol delivery, which would not apply to the broad treatment methods encompassed in the claims. Further, the compositions used in the examples do not include a composition comprising a nucleic acid directed to a common subunit of IL-3, IL-5 and GM-CSF receptors and at least one

oligonucleotide directed against CCR3 receptor. It is unclear whether the aerosol delivery in the examples would extrapolate to the claimed compositions. For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Further complicating the treatment methods claimed is the requirement of delivery of two separate oligonucleotides, each at a concentration effective to produce a treatment effect.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver a nucleic acid directed to a common subunit of IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against CCR3 receptor to generally any cell type to provide a treatment for the broad range of diseases encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would

include the determination of what specific allergies, cancers and inflammatory conditions can be treated with a nucleic acid directed to a common subunit of IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against CCR3 receptor, what specific cells to target for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in inhibition of the expression of IL-3, IL-5 and GM-CSF receptors and CCR3 receptor, to a level sufficient to result in a pharmaceutical effect or to treat a disease. Even for aerosol delivery, the skilled artisan would need to determine how to deliver an effective concentration of both antisense molecules and determine which antisense targeted to IL-3, IL-5 and GM-CSF receptors and CCR3 receptor are effective in vivo, or if this combination of antisense can produce a pharamaceutical treatment effect for the broad range of diseases encompassed in the claims. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods of treatment and the lack of working

examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claims 52-55 and 69-72 are over the full scope claimed without undue trial and error experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
May 5, 2003

Karen A. Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER